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(54) Heterocyclcarbonyl substituted benzofuranyl- and -thiophenyl-alkanecarboxyclic acid  
derivatives

Heterocyclcarbonylsubstituierte Benzofuranyl- und -thiophenylalkancarbonsäurederivate

Dérivés d'acides benzofuranyle- et benzothiophényle alcyclcarboxyliques substitués par des groupes  
hétérocyclcarbonyle

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EP-A-0 146 243

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## Remarks:

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**Description**

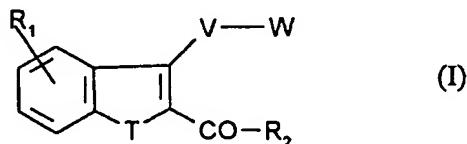
The invention relates to heterocycl carbonyl substituted benzofuran-alkanecarboxyclic acid derivatives, processes for their preparation and their use in medicaments.

5 It is known that the NADPH oxidase of phagocytes is the physiological source to the superoxide radical anion and reactive oxygen species derived therefrom which are important in the defence against pathogens. Uncontrolled formation leads to tissue damage in inflammatory processes. It is additionally known that elevation of phagocyte cyclic AMP leads to inhibition of oxygen radical production and that this cell function is more sensitive than others such as aggregation or enzyme release (cf. Inb. Arch. Allergy Immunol., vol. 97: pp 194-199, 1992).

10 Benzofuran- and benzo thiophene derivatives having lipoxygenase-inhibiting action are described in the publication EP 146 243.

Surprisingly it was found that compounds given by the general formula (I) inhibited oxygen radical formation and elevated cellular cyclic AMP levels probably by inhibition of phagocyte phosphodiesterase activity.

15 The invention relates to heterocycl carbonyl substituted benzofuranyl-and thiophenyl-alkanecarboxyclic acids derivatives of the general formula (I)



in which

25  $R^1$  represents hydrogen, halogen, carboxyl, cyano, nitro, trifluoromethyl or a group of a formula  $-OR^3$  or  $-SR^4$ ,

in which

30  $R^3$  and  $R^4$  are identical or different and denote cycloalkyl having 3 to 6 carbon atoms, hydrogen, a 5 to 7-membered saturated or unsaturated heterocycle having up to 4 heteroatoms from the series comprising N, S and/or O, which is optionally substituted by identical or different substituents from the series comprising halogen, cyano, nitro or by straight-chain or branched alkyl having up to 6 carbon atoms or

35 denote straight-chain or branched alkyl or alkenyl each having up to 8 carbon atoms, and each of which is optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising trifluoromethyl, halogen, cyano, carboxy, hydroxy, straight-chain or branched

alkoxy, alkoxy carbonyl or acyl each having up to 6 carbon atoms or by a 5- to 7-membered saturated

or unsaturated heterocycle having up to 4 hetero atoms from the series comprising N, S and O and to which an aromatic ring can be fused,

40 or by phenyl, wherein all rings are optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising nitro, halogen, carboxy or straight-chain or branched alkyl or alkoxy carbonyl each having up to 6 carbon atoms,

or alkyl or alkenyl are substituted by a group of formula  $-CO-NR^5R^6$

45  $R^5$  and  $R^6$  in which

are identical or different and denote phenyl, benzyl, hydrogen, formyl, straight-chain or branched alkyl or alkenyl each having up to 6 carbon atoms and which are optionally substituted by carboxy, hydroxy, straight-chain or branched alkoxy carbonyl having up to 6 carbon atoms,

or

50  $R^3$  denotes a hydroxyl protecting group,

$T$  represents an oxygen or sulfur atom

$V$  represents a straight-chain or branched alkylene or alkenylene chain each having 2 to 8 carbon atoms,

55  $W$  represents cyano, 1H-tetrazolyl or a group of a formula  $-CO-R^7$ ,  $-CO-NR^8R^9$ ,  $-CONR^{10}-SO_2-R^{11}$  or  $PO(OR^{12})(OR^{13})$ ,

in which

$R^7$  denotes hydroxyl, cycloalkyloxy having up 3 to 7 carbon atoms or straight-chain or branched alkoxy having up to 8 carbon atoms,

- 5      R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> are identical or different and denote hydrogen, phenyl, benzyl, straight-chain or branched alkyl or acyl each having up to 6 carbon atoms and which are optionally substituted by hydroxyl, or
- 5      R<sup>8</sup> and R<sup>9</sup> denote hydroxyl,
- 5      R<sup>11</sup> denotes a straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by phenyl or trifluoromethyl, or
- 10     R<sup>12</sup> and R<sup>13</sup> denotes phenyl, which is optionally substituted by substituents from the series comprising halogen, cyano, nitro or by straight-chain or branched alkyl having up to 6 carbon atoms,
- 10     R<sup>12</sup> and R<sup>13</sup> are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,
- 15     R<sup>2</sup> represents a 5 to 7 membered, saturated or unsaturated heterocycle, which can contain up to three oxygen, sulphur and/or nitrogen atoms as heteroatoms and to which further a benzene ring can be fused and wherein both rings are optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising hydroxyl, halogen, nitro, 1H-tetrazolyl, trifluoromethyl, trifluoromethoxy, difluoromethyl, difluoromethoxy, cyano, carboxy, straight-chain or branched alkyl, alkoxy, alkoxy carbonyl or acyl each having up to 8 carbon atoms or by a group of formula -NR<sup>14</sup>R<sup>15</sup>, -SR<sup>16</sup>, SO<sub>2</sub>R<sup>17</sup> or -O-SO<sub>2</sub>R<sup>18</sup>,
- 15     in which
- 20     R<sup>14</sup> and R<sup>15</sup> have the first meaning shown above for R<sup>8</sup> and R<sup>9</sup> and are identical to the latter or different from the latter,
- 20     R<sup>16</sup> denotes straight-chain or branched alkyl having up to 6 carbon atoms,
- 20     R<sup>17</sup> and R<sup>18</sup> are identical or different and represent straight-chain or branched alkyl having up to 6 carbon atoms, benzyl or phenyl, which are optionally substituted by trifluoromethyl, halogen or straight-chain or branched alkyl having up to 6 carbon atoms,
- 25     and salts thereof.

The heterocyclcarbonyl substituted benzofuranyl- and thiophenyl-alkanecarboxylic acid derivatives according to the invention can also be present in the form of their salts. In general, salts with organic or inorganic bases or acids may be mentioned here.

Physiologically acceptable salts are preferred in the context of the present invention. Physiologically acceptable salts of the heterocyclcarbonyl substituted benzofuranyl- and thiophenyl-alkanecarboxylic acid derivatives can be metal or ammonium salts of the substances according to the invention, which contain a free carboxylic group. Those which are particularly preferred are, for example, sodium, potassium, magnesium or calcium salts, and also ammonium salts which are derived from ammonia, or organic amines, such as, for example, ethylamine, di- or triethylamine, di- or triethanolamine, dicyclohexylamine, dimethylaminoethanol, arginine, lysine or ethylenediamine.

Physiologically acceptable salts can also be salts of the compounds according to the invention with inorganic or organic acids. Preferred salts here are those with inorganic acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulphuric acid, or salts with organic carboxylic or sulphonic acids such as, for example, acetic acid, maleic acid, fumaric acid, malic acid, citric acid, tartaric acid, ethanesulphonic acid, benzenesulphonic acid, toluenesulphonic acid or naphthalenedisulphonic acid.

The compounds according to the invention can exist in stereoisomeric forms which either behave as image and mirror image (enantiomers), or which do not behave as image and mirror image (diastereomers). The invention relates both to the antipodes and to the racemate forms, as well as the diastereomer mixtures. The racemate forms, like the diastereomers, can be separated into the stereoisomerically uniform constituents in a known manner.

Hydroxyl protective group in the context of the above-mentioned definition in general represents a protective group from the series comprising: trimethylsilyl, tert.butyl-dimethylsilyl, benzyl, 4-nitrobenzyl, 4-methoxybenzyl, acetyl, tetrahydropyranyl and benzoyl.

Heterocycle in general represents a 5- to 7-membered saturated or unsaturated, preferably 5- to 6- membered, saturated or unsaturated ring which can contain up to 4 oxygen, sulphur and/or nitrogen atoms as heteroatoms and to which further benzene ring can be fused.

The following are mentioned as preferred: thienyl, furyl, pyrrolyl, 1,2-thiazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, quinazolyl, quinoxazolyl, cinnolyl, thiazolyl benzothiazolyl, isothiazolyl, benzisothiazolyl, oxazolyl, benzoxazolyl, isoxazolyl, imidazolyl, benzimidazolyl, benzo[b]thiophenyl, indolyl, morpholinyl, pyrrolidinyl, piperidyl, piperazinyl, oxazolyl, oxazolinyl, triazolyl or tetrazolyl.

Preferred compounds of the general formula (I) are those in which

5	<b>R<sup>1</sup></b>	represents hydrogen, fluorine, chlorine, bromine, nitro, trifluoromethyl or a group of a formula -OR <sup>3</sup> or -SR <sup>4</sup> , in which
10	<b>R<sup>3</sup> and R<sup>4</sup></b>	are identical or different and denote hydrogen, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, chinolyl, pyridyl, imidazolyl, 1,3-thiazolyl or thienyl, which are optionally substituted by identical or different substituents from the series comprising fluorine, chlorine, bromine, iodine, cyano, nitro or by straight-chain or branched alkyl having up to 5 carbon atoms or
15		denote straight-chain or branched alkyl or alkenyl each having up to 6 carbon atoms, and each of which is optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising trifluoromethyl, fluorine, chlorine, bromine, iodine, cyano, carboxy, hydroxy, straight-chain or branched alkoxy, alkoxy carbonyl or acyl each having up to 5 carbon atoms or by chinolyl, pyridyl, pyrazolyl, 1,3-thiadiazolyl, thienyl, imidazolyl or N-methyl-substituted imidazolyl and to which benzene can be fused,
20		or by phenyl, where in all rings are optionally monosubstituted to disubstituted by identical or different substituents from the series comprising nitro, fluorine, chlorine, bromine, iodine, carboxy or straight-chain or branched alkyl or alkoxy carbonyl each having up to 5 carbon atoms, or alkyl or alkenyl are substituted by a group of formula -CO-NR <sup>5</sup> R <sup>6</sup>
25	<b>R<sup>5</sup> and R<sup>6</sup></b>	in which
30		are identical or different and denote phenyl, benzyl, hydrogen, formyl, straight-chain or branched alkyl or alkenyl each having up to 5 carbon atoms, which are optionally substituted by carboxy, hydroxy or straight-chain or branched alkoxy carbonyl having up to 4 carbon atoms,
35	<b>R<sup>3</sup></b>	or
	<b>T</b>	denotes acetyl, benzyl or tetrahydrofuryl,
40	<b>V</b>	represents an oxygen or sulfur atom
45	<b>W</b>	represents a straight-chain or branched alkylene or alkenyl chain each having 2 to 6 carbon atoms, represents cyano, 1H-tetrazolyl or a group of a formula -CO-R <sup>7</sup> , -CO-NR <sup>8</sup> R <sup>9</sup> , -CONR <sup>10</sup> -SO <sub>2</sub> -R <sup>11</sup> or PO(OR <sup>12</sup> )(OR <sup>13</sup> ),
50	<b>R<sup>7</sup></b>	in which
55	<b>R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup></b>	denotes hydroxyl, cyclopropyl oxy, cyclopentyl oxy, cyclohexyl oxy or straight-chain or branched alkoxy having up to 6 carbon atoms,
60		are identical or different and denote hydrogen, benzyl, phenyl, straight-chain or branched alkyl or acyl each having up to 4 carbon atoms and which are optionally substituted by hydroxyl,
65	<b>R<sup>8</sup> or R<sup>9</sup></b>	or
70	<b>R<sup>11</sup></b>	denote hydroxyl,
75		denotes straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by phenyl or trifluoromethyl,
80		or
85	<b>R<sup>12</sup> and R<sup>13</sup></b>	denotes phenyl, which is optionally substituted by substituents from the series comprising fluorine, chlorine, bromine, iodine, cyano, nitro or by straight-chain or branched alkyl having up to 4 carbon atoms,
90		are identical or different and represents hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,
95	<b>R<sup>2</sup></b>	represents pyridyl, pyrryl, imidazolyl, pyrazolyl, thienyl, isothiazolyl, 1,3-thiazolyl or benzo[b]thiophenyl, wherein both rings are optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising hydroxyl, fluorine, chlorine, bromine, iodine, nitro, tetrazolyl, trifluoromethyl, trifluoromethoxy, difluoromethyl, difluoromethoxy, cyano, carboxy, straight-chain or branched alkyl, alkoxy, alkoxy carbonyl or acyl each having up to 6 carbon atoms or by a group of formula -NR <sup>14</sup> R <sup>15</sup> , -SR <sup>16</sup> , -SO <sub>2</sub> R <sup>17</sup> or -O-SO <sub>2</sub> R <sup>18</sup> ,
100		in which
105	<b>R<sup>14</sup> and R<sup>15</sup></b>	have the first meaning shown above for R <sup>8</sup> and R <sup>9</sup> and are identical to the latter or different from the latter,
110	<b>R<sup>16</sup></b>	denotes straight-chain or branched alkyl having up to 4 carbon atoms,
115	<b>R<sup>17</sup> and R<sup>18</sup></b>	are identical or different and represent straight-chain or branched alkyl having up to 5 carbon atoms or phenyl, which is optionally substituted by trifluoromethyl, fluorine, chlorine, bromine or straight-chain or branched alkyl having up to 3 carbon atoms, and salts thereof.

Particularly preferred compounds of the general formula (I) are those

in which

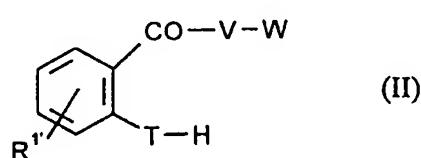
- 5      R<sup>1</sup>      represents hydrogen, fluorine, chlorine, bromine, nitro, trifluoromethyl or a group of a formula -OR<sup>3</sup> or -SR<sup>4</sup>,  
       in which
- 10     R<sup>3</sup>      denotes hydrogen, tetrahydropyanyl, benzyl, acetyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, chinolyl, pyridyl, imidazolyl or thienyl, which are optionally substituted by identical or different substituents from the series comprising fluorine, chlorine, bromine, cyano, nitro or by straight-chain or branched alkyl having up to 4 carbon atoms or  
       denotes straight-chain or branched alkyl or alkenyl each having up to 5 carbon atoms, and each of which is optionally monosubstituted to disubstituted by identical or different substituents from the series comprising trifluoromethyl, fluorine, chlorine, bromine, cyano, carboxy, hydroxy, straight-chain or branched alkoxy, alkoxy carbonyl or acyl each having up to 4 carbon atoms or by chinolyl, pyridyl, imidazolyl or N-methyl-substituted imidazolyl and to which benzene can be fused,  
       or by phenyl, wherein all rings are optionally monosubstituted to disubstituted by identical or different substituents from the series comprising nitro, fluorine, chlorine, bromine, carboxy or straight-chain or branched alkyl, alkoxy carbonyl each having up to 4 carbon atoms, or alkyl or alkenyl are substituted by a group of formula -CO-NR<sup>5</sup>R<sup>6</sup>  
       in which
- 20     R<sup>5</sup> and R<sup>6</sup>      are identical or different and denote phenyl, benzyl, hydrogen, formyl, straight-chain or branched alkyl each having up to 4 carbon atoms, which are optionally substituted by carboxy, hydroxy or straight-chain or branched alkoxy carbonyl having up to 3 carbon atoms.
- 25     R<sup>4</sup>      denotes straight-chain or branched alkyl having up to 4 carbon atoms,  
       T      represents an oxygen atom or sulphur  
       V      represents a straight-chain or branched alkylene or alkenylene chain having 2 to 5 carbon atoms,  
       W      represents cyano, 1H-tetrazolyl or a group of a formula -CO-R<sup>7</sup> or -CO-NR<sup>8</sup>R<sup>9</sup>,  
       in which
- 30     R<sup>7</sup>      denotes hydroxyl, cyclopropoxy, cyclopentyloxy, cyclohexyloxy or straight-chain or branched alkoxy having up to 5 carbon atoms,  
       R<sup>8</sup> and R<sup>9</sup>      are identical or different and denote phenyl, benzyl, hydrogen, straight-chain or branched alkyl or acyl each having up to 4 carbon atoms,

and

- 35     R<sup>2</sup>      represents pyridyl, pyrryl, furyl, thienyl, 1,3-thiazolyl or benzo[b]thiophenyl, which are optionally mono-substituted to trisubstituted by identical or different substituents from the series comprising, hydroxyl, fluorine, chlorine, bromine, nitro, tetrazolyl, trifluoromethyl, trifluoromethoxy, difluoromethyl, difluoromethoxy, cyano, carboxy, straight-chain or branched alkyl, alkoxy, alkoxy carbonyl or acyl each having up to 5 carbon atoms or by a group of formula -NR<sup>14</sup>R<sup>15</sup>, SR<sup>16</sup> or -SO<sub>2</sub>R<sup>17</sup>,  
       in which
- 40     R<sup>14</sup> and R<sup>15</sup>      have the meaning of R<sup>8</sup> and R<sup>9</sup>,  
       R<sup>16</sup>      denotes straight-chain or branched alkyl having up to 3 carbon atoms,  
       R<sup>17</sup>      denotes straight-chain or branched alkyl having up to 3 carbon atoms or phenyl, and salts thereof.

45     A process for the preparation of the compounds of the general formula (I) has additionally been found, characterised in that  
       compounds of the general formula (II)

50



55

in which

T, V and W have the abovementioned meaning,

and

- 5 R<sup>1</sup> represents a group of formula -OR<sup>3</sup>,  
in which  
R<sup>3</sup> has the abovementioned meaning of R<sup>3</sup>, but does not represent hydrogen,

are reacted with compounds of the general formula (III)



in which

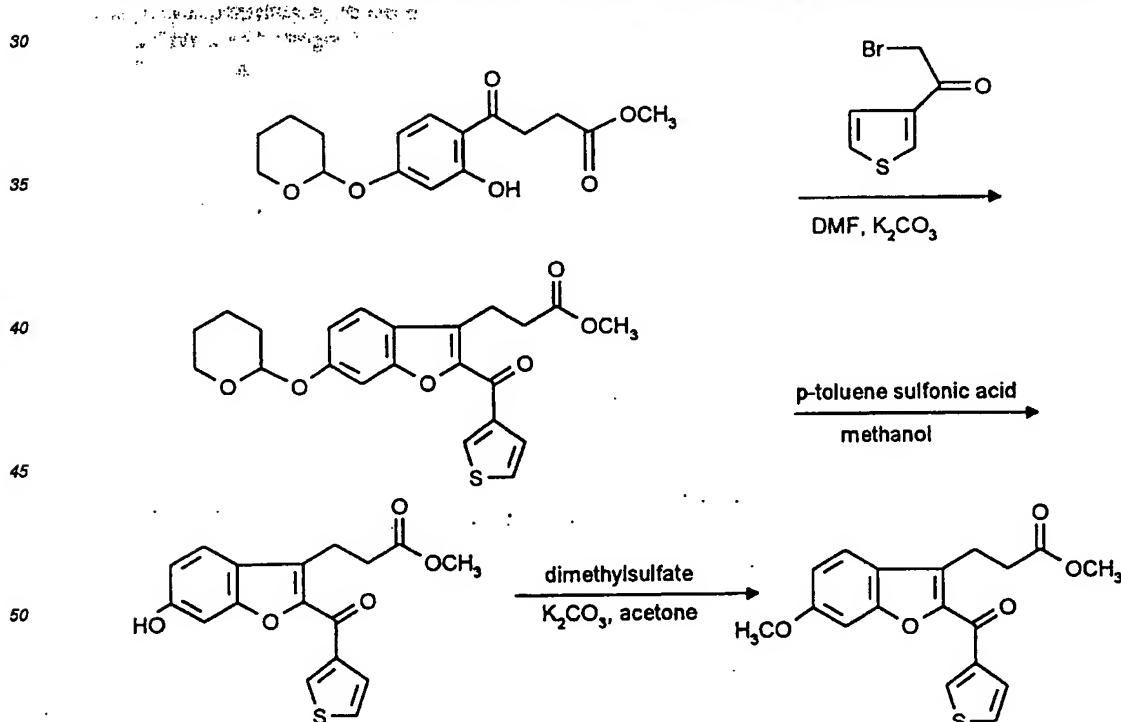
- 15 R<sup>2</sup> has the abovementioned meaning

and

- 20 Y represents a typical leaving group such as, for example, chlorine, bromine, iodine, tosylate or mesylate, prefera-  
bly bromine,

25 in inert solvents and in the presence of a base  
and, then, if appropriate, the protective groups are split off,  
the esters are hydrolysed, the acids are esterified with the appropriate alcohols in the presence of a catalyst or the com-  
pounds are alkylated  
or the esters are directly reacted with amines or the free carboxylic acids, if appropriate in the presence of above and/or  
an auxiliary, an amidation or sulfonamidation follows.

The process according to the invention can be illustrated by way of example by the following equations:



Suitable solvents are generally customary organic solvents which do not change under the reaction conditions.

These include ethers such as diethyl ether, dioxane or tetrahydrofuran, acetone, dimethylsulfoxide, dimethylformamide or alcohols such as methanol, ethanol, propanol or halogenohydrocarbons such as dichlormethane, trichloromethane or tetrachloromethane. Dimethylformamide and dichloromethane are preferred.

Suitable bases are generally inorganic or organic bases. These preferably include alkali metal hydroxides such as, for example, sodium hydroxide, sodium hydrogencarbonate or potassium hydroxide, alkaline earth metal hydroxides such as, for example, barium hydroxide, alkali metal carbonates such as sodium carbonate, potassium carbonate, alkaline earth metal carbonates such as calcium carbonate, or alkaline metal oder alkaline earth metal alkoxides such as sodium methoxide or potassium methoxide, sodium ethoxide or potassium ethoxide or potassium tert.-butoxide, or organic amines (trialkyl(C<sub>1</sub>-C<sub>6</sub>)amines) such as triethylamine, or heterocycles such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or amides such as sodium amides, lithium butyl amide or butyl-lithium, pyridine or methylpiperidine. It is also possible to employ alkali metals, such as sodium or its hydrides such as sodium hydride, as bases. Potassium carbonate, triethylamine, sodium hydrogencarbonate and sodiumhydroxide are preferred.

The process is in general carried out in a temperature range from +10°C to +150°C, preferably from +20°C to +60°C.

The process is generally carried out at normal pressure. However, it is also possible to carry out it at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

The base is employed in an amount from 1 mol to 10 mol, preferably from 1.0 mol to 2.1 mol, relative to 1 mol of the compounds of the general formula (III).

The compounds of the general formula (II), (III) (IV) and (V) are known or can be prepared by published methods.

The compounds according to the invention specifically inhibit the production of superoxide by polymorphonuclear leucocytes (PMN) without impairing other cell functions such as degranulation or aggregation. The inhibition was mediated by the elevation of cellular cAMP probably due to inhibition of the type IV phosphodiesterase responsible for its degradation

They can therefore be employed in medicaments for controlling acute and chronic inflammatory processes.

The compounds according to the invention are preferably suitable for the treatment and prevention of acute and chronic inflammations of the airways, such as emphysema, alveolitis, shock lung, asthma, bronchitis, arteriosclerosis, arthrosis, inflammations of the gastro-intestinal tract and myocarditis. The compounds according to the invention are additionally suitable for reducing the damage to infarct tissue after reoxygenation. In this case the simultaneous administration of allopurinol to inhibit xanthine oxidase is of advantage. Combination therapy with superoxide dismutase is also of use.

#### Test description

35 1. Preparation of human PMN

Blood was taken from healthy subjects by venous puncture and neutrophils were purified by dextran sedimentation and resuspended in the buffered medium.

2. Inhibition of FMLP-stimulated production of superoxide radical anions.

Neutrophils ( $2.5 \times 10^5 \text{ ml}^{-1}$ ) were mixed with cytochrome C (1.2 mg/ml) in the wells of a microtitre plate. Compounds according to the invention were added in dimethyl sulphoxide (DMSO). Compound concentration ranged from 2.5 nM to 10 µM, the DMSO concentration was 0.1% v/v in all wells. After addition of cytochalasin b (5 µg x ml<sup>-1</sup>) the plate was incubated for 5 min at 37°C. Neutrophils were then stimulated by addition of  $4 \times 10^{-8} \text{ M}$  FMLP and superoxide generation measured as superoxide dismutase inhibitable reduction of cytochrome C by monitoring the OD<sub>550</sub> in a Thermomax microtitre plate spectrophotometer. Initial rates were calculated using a Softmax kinetic calculation programme. Blank wells contained 200 units of superoxide dismutase.

The inhibition of superoxide production was calculated as follows:

$$\frac{[1 - ((Rx - Rb))]}{((Ro - Rb))} \cdot 100$$

55 Rx = Rate of the well containing the compound according to the invention.

Ro = Rate in the control well.

Rb = Rate in the superoxide dismutase containing blank well.

3. Measurement of PMN cyclic AMP concentration

The compounds according to the invention were incubated with  $3.7 \times 10^6$  PMN for 5 min at 37°C before addition of  $4 \times 10^{-8}$  M FMLP. After 6 min protein was precipitated by the addition of 1% v/v conc. HCl in 96% v/v ethanol containing 0.1 mM EDTA. After centrifugation the ethanolic extracts were evaporated to dryness under N<sub>2</sub> and resuspended in 50 mM Tris/HCl pH 7.4 containing 4 mM EDTA. The cyclic AMP concentration in the extracts was determined using a cyclic AMP binding protein assay supplied by Amersham International plc. Cyclic AMP concentrations were expressed as percentage of vehicle containing control incubations.

4. Assay of PMN phosphodiesterase

PMN suspensions ( $10^7$  cells/ml) were sonicated for 6 x 10 sec on ice. Aliquots (100 µl) were incubated for 5 min at 37°C with the compounds according to the invention or vehicle before the addition of <sup>3</sup>H-cAMP (1 mM and 200 nCi per incubation). After 20 min the reaction was stopped by heating at 100°C for 45 seconds. After cooling 100 mg of 5'-nucleotidase was added to each tube and the samples incubated for 15 min at 37°C. The conversion to <sup>3</sup>H-adenosine was determined by ion-exchange chromatography on Dowex AG-1x (chloride form) followed by liquid scintillation counting. Percentage inhibition was determined by comparison to vehicle containing controls.

5. Effect of intravenously administered compounds on the FMLP-induced skin oedema guinea pigs

Guinea pigs (600 - 800 g) were anaesthetized with pentobarbitone sodium (40 mg/kg, i.p.) and injected (i.v.) with a 0.5 ml mixture of pontamine sky blue (5% w/v) and <sup>125</sup>I-HSA (1 µl/animal). 10 minutes later 3 intradermal injections of FMLP (10 µg/site), 1 injection of histamine (1 µg/site) and 1 injection of vehicle (100 µl of 0.2% DMSO v/v in Hanks Buffered salt solution) were made on the left hand side of the animal (preinjection sites). 5 minutes later the drug (1 ml/kg) or the vehicle (50% PEG 400 V/V in distilled water, 1 mg/kg) was administered (i.v.). 10 minutes later an identical pattern of interadermal injections was made on the opposite flank of the animal (post-injection sites). These responses were allowed to develop for 15 minutes before the animal was sacrificed and a blood sample taken.

Skin sites and plasma samples were counted for 1 minute on a gamma counter and the degree of oedema calculated as µl plasma/skin site. Statistical analysis was done by a paired t-test on the mean of the 3 preinjection site values of µl plasma obtained for FMLP/animal. The percentage inhibition of drug or vehicle was calculated as follow

$$\frac{X \mu\text{l plasma (post-injection site)}}{X \mu\text{l plasma (pre-injection site)}} \times 100$$

6. Effect of orally administered compounds on the FMLP-induced skin oedema of guinea-pigs  
*in vivo Test's p.o.*

Guinea-pigs (600-800 g) were fasted overnight and orally treated with vehicle (1% Tylose w/v at 5 ml/kg) or drug (10 mg/kg; 2 mg/ml in 1% Tylose at 5 ml/kg) 40 minutes later the animals were anaesthetized with pentobarbitone sodium (40 mg/kg, i.P.) and 0.6 ml of a mixture of pontamine sky blue (5% w/v) and <sup>125</sup>I-HSA (1 µ ci/animal) was injected (i.v.). 90 minutes after oral pretreatment FMLP (50 µg/site) was injected (i.d.) at 4 different sites, histamine (1 µg/site) and vehicle (100 µl, 1% DMSO v/v in Hanks buffered salt solution) were both injected (i.d.) at 2 different sites.

The responses were allowed to develop for 30 minutes before the animal was sacrificed and a blood sample taken. Skin sites and plasma samples were counted for 1 minute on a gamma counter. The degree of oedema was calculated as µl plasma/skin site. Statistical analysis was carried out by a Mann-Whitney U-test on the mean of the 4 values of µl Plasma obtained for FMLP/animal.

The new active compounds can be converted in a known manner into the customary formulations, such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions and solutions, using inert, nontoxic, pharmaceutically suitable excipients or solvents. In this connection, the therapeutically active compound should in each case be present in a concentration of about 0.5 to 90% by weight of the total mixture, i.e. in amounts which are sufficient in order to achieve the dosage range indicated.

The formulations are prepared, for example, by extending the active compounds with solvents and/or excipients, if appropriate using emulsifiers and/or dispersants, where, for example, in the case of the use of water as a diluent, organic solvents can be used as auxiliary solvents if appropriate.

Administration is carried out in a customary manner, preferably orally or parenterally, in particular perlingually or intravenously.

In the case of parenteral administration, solutions of the active compound can be employed using suitable liquid vehicles.

In general, it has proved advantageous on intravenous administration to administer amounts from about 0.001 to 10 mg/kg, preferably about 0.01 to 5 mg/kg of body weight to achieve effective results, and on oral administration the dosage is about 0.01 to 25 mg/kg, preferably 0.1 to 10 mg/kg of body weight.

In spite of this, it may be necessary to depart from the amounts mentioned, in particular depending on the body weight or the type of application route, on individual behaviour towards the medicament, the manner of its formulation and the time or interval at which administration takes place. Thus, in some cases it may be sufficient to manage with less than the abovementioned minimum amount, while in other cases the upper limit mentioned must be exceeded. In the case of administration of relatively large amounts, it is advisable to divide these into several individual doses over the course of the day.

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### Solvents

- I petrolether : ethylacetate 1:1
- II petrolether : ethylacetate 5:1
- 15 III petrolether : ethylacetate 5:2
- IV dichlormethane : methanol 95:5
- V dichlormethane : methanol 9:1
- VI dichlormethane
- DMF dimethylformamide

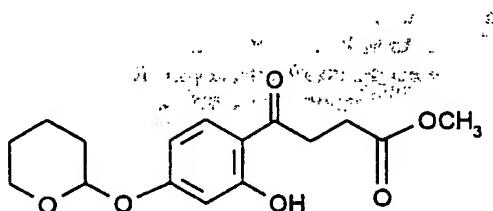
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### Starting compounds

#### Example I

25 2'-Hydroxy-3-oxo-4'-(tetrahydro-2H-pyran-2-yl)oxy]benzenebutanoic acid methylester

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20.0 g (0.089 mol) 2',4'-Dihydroxy-3-oxo-benzenebutanoic acid methylester were dissolved in 200 ml dichloromethane / tetrahydrofuran (95:5) and 9.2 ml (0.1 mol) 3,4-dihydro-2H-pyran and 10 mg p-toluenesulfonic acid were added successively. The suspension was stirred at room temperature for 1 hour. 400 ml of a NaHCO<sub>3</sub> solution were added, the organic layer separated and washed three times with water. The organic phase was dried using Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The residue was recrystallised from diethylether.

40

Yield: 13.4 g (49% of theory)

R<sub>f</sub> = 0,55, I

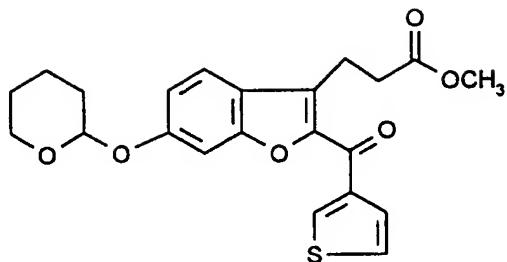
45 Preparation Examples

#### Example 1

50 6-[(Tetrahydro-2H-pyran-2-yl)oxy]-2-(3-thienylcarbonyl)-3-benzofuranpropanoic acid methylester

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Equivalent amounts, 1.5 g (4.9 mmol) of 2'-Hydroxy-3-oxo-4'-(tetrahydro-2H-pyran-2-yl)oxy]benzenebutanoic acid, 15 methylester and 1.0 g (4.9 mmol) of 2-bromo-1-(3-thienyl)ethanone were dissolved in 50 ml acetone and 1.35 g (9.7 mol) of potassium carbonate were added. The suspension was heated under reflux for 16 hours. The mixture was filtered, the solvent was distilled off in vacuo and the residue was taken up in ethylacetate. The organic phase was washed three times with water, one time with a NaCl solution, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The residue was further purified by chromatography (silica gel 60).

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Yield: 0.83 g (41%)

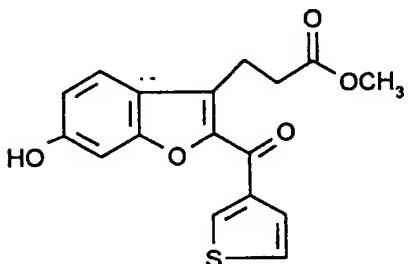
R<sub>f</sub> = 0.43, II

#### Example 2

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#### 6-Hydroxy-2-(3-thienylcarbonyl)-3-benzofuranpropanoic acid methylester

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0.7 g (1.7 mmol) of 6-[(tetrahydro-2H-pyran-1-yl)oxy]-2-(3-thienylcarbonyl)-3-benzofuranpropanoic acid methylester were dissolved in 30 ml methanol and 5 mg p-toluenesulfonic acid were added. The suspension was stirred at r.t. for 2 hours. The solvent was distilled off, the residue solved in ethylacetate and washed two times with water, once with a Na<sub>2</sub>HCO<sub>3</sub> solution and once with a NaCl solution. The organic layer was dried using Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo and the residue was further purified by chromatography (silica gel 60).

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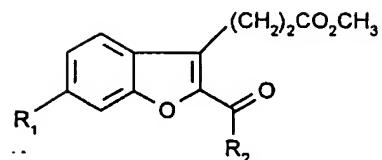
Yield: 0.4 g (72%)

R<sub>f</sub> = 0.25, II

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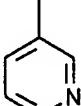
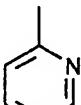
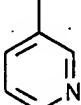
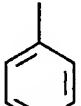
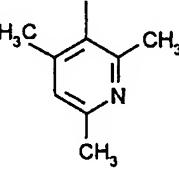
The compounds shown in Table 1 were prepared in analogy to the procedure of Example 2:

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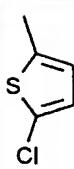
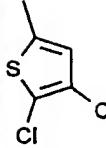
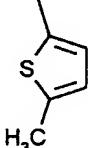
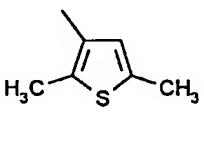
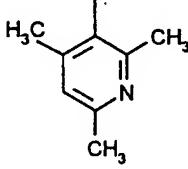
**Table 1:**

Example No.	R <sup>1</sup>	R <sup>2</sup>	R <sub>f</sub>	Yield (% of theory)
15 3	-OH		0.55 (III)	70
20 4	-OH		0.34 (I)	71.1
25 5	-OH		0.26 (I)	91.2
30 6	-OH		0.18 (I)	84.4
35 45 50 7	-OCH <sub>2</sub> -CO <sub>2</sub> CH <sub>3</sub>		0.39 (I)	78

**Table 1:** (continuation)

Example No.	R <sup>1</sup>	R <sup>2</sup>	R <sub>f</sub>	Yield (% of theory)
8	-O-CH <sub>2</sub> -CO-OCH <sub>3</sub>		0.34 (I)	47.2
9	-O-CH-COHN <sub>2</sub>		0.15 (I)	59.3
10	-O-CH <sub>2</sub> -CONH <sub>2</sub>		0.13 (I)	55.4
11	-O-CH <sub>2</sub> -CONH <sub>2</sub>		0.41 (V)	76.2
12	-OH		0.45 (V)	94.1

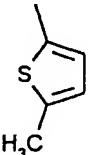
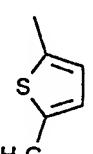
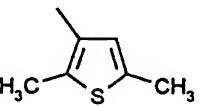
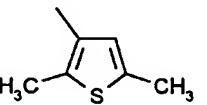
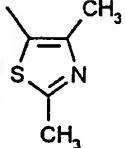
**Table 1:** (continuation)

Example No.	R <sup>1</sup>	R <sup>2</sup>	R <sub>f</sub>	Yield (% of theory)
13	-OH		0.35 (III)	74.6
14	-OH		0.30 (III)	86.9
15	-OH		0.25 (III)	83.0
16	-OH		0.32 (III)	85.7
17	-O-CH <sub>2</sub> -CO-OCH <sub>3</sub>		0.63 (V)	94.4

**Table 1:** (continuation)

	Example No.	R <sup>1</sup>	R <sup>2</sup>	R <sub>f</sub>	Yield (% of theory)
5	18	-O-CH <sub>2</sub> -CONH <sub>2</sub>		0.35 (V)	98.9
10	19	-O-CH <sub>2</sub> -CO-OCH <sub>3</sub>		0.34 (III)	87.0
15	20	-O-CH <sub>2</sub> -CONH <sub>2</sub>		0.55 (V)	91.6
20	21	-O-CH <sub>2</sub> -CO-OCH <sub>3</sub>		0.41 (III)	71.4
25	22	-O-CH <sub>2</sub> -CONH <sub>2</sub>		0.58 (V)	98.2
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35					
40					
45					
50					

**Table 1:** (continuation)

Example No.	R <sup>1</sup>	R <sup>2</sup>	R <sub>f</sub>	Yield (% of theory)
23	-O-CH <sub>2</sub> -CO-OCH <sub>3</sub>		0.45 (III)	93.6
24	-O-CH <sub>2</sub> -CONH <sub>2</sub>		0.62 (V)	90.9
25	-O-CH <sub>2</sub> -CO-OCH <sub>3</sub>		0.38 (III)	89.4
26	-O-CH <sub>2</sub> -CONH <sub>2</sub>		0.60 (V)	98.7
27	-O-CH <sub>2</sub> -CO-OCH <sub>3</sub>		0.55 (III)	86.4

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**Table 1:** (continuation)

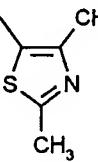
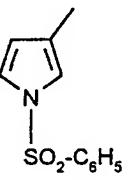
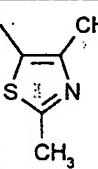
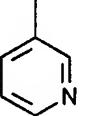
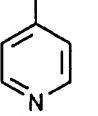
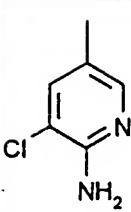
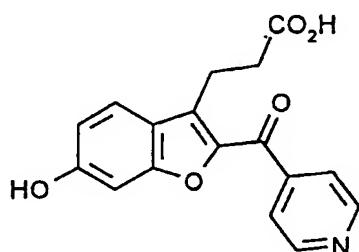
Example No.	R <sup>1</sup>	R <sup>2</sup>	R <sub>f</sub>	Yield (% of theory)
28	-O-CH <sub>2</sub> -CONH <sub>2</sub>		0.11 (III)	quant.
29	-OH		0.08 (II)	quant.
30	-OH		0.47 (III)	98.2
31	-Cl		0.56 (III)	16.4
32	-Cl		0.58 (III)	7.8

Table 1: (continuation)

Example No.	R <sup>1</sup>	R <sup>2</sup>	R <sub>f</sub>	Yield (% of theory)
33	-OH		0.34 (I)	70

Example 34

6-hydroxy-2-(4-pyridyl)-3-benzofuran-propanoic acid

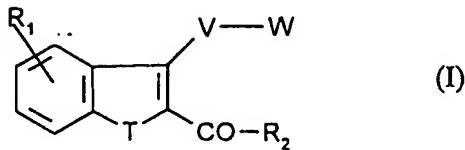


1.5 g (4.6 mmol) of the compound from starting compounds Example III were dissolved in 50 ml methanol/tetrahydrofuran (1:1) and 5.5 ml of a 2 NaOH solution were added. The mixture was stirred at room temperature for 24 hours, dissolved in water and acidified with 1 N hydrochloric acid. The precipitate was filtered off, washed several times with water and dried in vacuo. The further reaction was carried out as described in Example 1.

Yield: 1.25 g (87%)  
R<sub>f</sub>: 0.01 (IV)

**Claims**

1. Heterocyclylcarbonyl substituted benzofuranyl- and thiophenyl-alkanecarboxylic acid derivatives of the general formula (I)



in which

10       $R^1$       represents hydrogen, halogen, carboxyl, cyano, nitro, trifluoromethyl or a group of a formula -  
OR<sup>3</sup> or -SR<sup>4</sup>,

in which

15       $R^3$  and  $R^4$       are identical or different and  
denote cycloalkyl having 3 to 6 carbon atoms, hydrogen, a 5 to 7-membered saturated or unsaturated heterocycle having up to 4 heteroatoms from the series comprising N, S and O, which is optionally substituted by identical or different substituents from the series comprising halogen, cyano, nitro or by straight-chain or

20      branched alkyl having up to 6 carbon atoms or denote straight-chain or branched alkyl or alkenyl each having up to 8 carbon atoms, and each of which is optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising trifluoromethyl, halogen, cyano, carboxy, hydroxy, straight-chain or branched alkoxy, alkoxy carbonyl or acyl each having up to 6 carbon atoms or by a 5- to 7-membered saturated or unsaturated heterocycle having up to 4 hetero atoms from the series comprising N, S and O and to which an aromatic ring can be fused,

25      or by phenyl, wherein all rings are optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising nitro, halogen, carboxy or straight-chain or branched alkyl or alkoxy carbonyl each having up to 6 carbon atoms,

30      or alkyl or alkenyl are substituted by a group of formula -CO-NR<sup>5</sup>R<sup>6</sup>

in which

35       $R^5$  and  $R^6$       are identical or different and  
denote phenyl, benzyl, hydrogen, formyl, straight-chain or branched alkyl or alkenyl each having up to 6 carbon atoms and which are optionally substituted by carboxy, hydroxy, straight-chain or branched alkoxy carbonyl having up to 6 carbon atoms,

or

40       $R^3$       denotes a hydroxyl protecting group from the series comprising: trimethylsilyl, tert.butyl-dimethylsilyl, benzyl, 4-nitrobenzyl, 4-methoxybenzyl, acetyl, tetrahydropyranyl and benzoyl,

$T$       represents an oxygen or sulfur atom

45       $V$       represents a straight-chain or branched alkylene or alkenylene chain each having 2 to 8 carbon atoms,

$W$       represents cyano, 1H-tetrazolyl or a group of a formula -CO-R<sup>7</sup>, -CO-NR<sup>8</sup>R<sup>9</sup>, -CONR<sup>10</sup>-SO<sub>2</sub>-R<sup>11</sup> or PO(OR<sup>12</sup>)(OR<sup>13</sup>),

in which

50       $R^7$       denotes hydroxyl, cycloalkyloxy having up 3 to 7 carbon atoms or straight-chain or branched alkoxy having up to 8 carbon atoms,

45       $R^8$ ,  $R^9$  and  $R^{10}$       are identical or different and denote hydrogen, phenyl, benzyl, straight-chain or branched alkyl or acyl each having up to 6 carbon atoms and which are optionally substituted by hydroxyl, or

55       $R^8$  and  $R^9$       denote hydroxyl,

$R^{11}$       denotes a straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by phenyl or trifluoromethyl,

or

55       $R^{12}$  and  $R^{13}$       denotes phenyl, which is optionally substituted by substituents from the series comprising halogen, cyano, nitro or by straight-chain or branched alkyl having up to 6 carbon atoms,

are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,

$R^2$       represents a 5 to 7 membered, saturated or unsaturated heterocycle, which can contain up to three oxygen, sulphur and/or nitrogen atoms as heteroatoms and to which further a benzene ring

can be fused and wherein both rings are optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising hydroxyl, halogen, nitro, 1H-tetrazolyl, trifluoromethyl, trifluoromethoxy, difluoromethyl, difluoromethoxy, cyano, carboxy, straight-chain or branched alkyl, alkoxy, alkoxy carbonyl or acyl each having up to 8 carbon atoms or by a group of formula -NR<sup>14</sup>R<sup>15</sup>, -SR<sup>16</sup>, SO<sub>2</sub>R<sup>17</sup> or -SO<sub>2</sub>-R<sup>18</sup>.

in which

R<sup>14</sup> and R<sup>15</sup> have the first meaning shown above for R<sup>8</sup> and R<sup>9</sup> and are identical to the latter or different from the latter,

R<sup>16</sup> denotes straight-chain or branched alkyl having up to 6 carbon atoms,

R<sup>17</sup> and R<sup>18</sup> are identical or different and represent straight-chain or branched alkyl having up to 6 carbon atoms, benzyl or phenyl, which are optionally substituted by trifluoromethyl, halogen or straight-chain or branched alkyl having up to 6 carbon atoms.

and salts thereof.

2. Heterocyclylcarbonyl substituted benzofuranyl and thiophenyl-alkanecarboxylic acid derivatives according to claim 1.

R<sup>1</sup> represents hydrogen, fluorine, chlorine, bromine, nitro, trifluoromethyl or a group of a formula -OR<sup>3</sup> or -SR<sup>4</sup>,

in which

R<sup>3</sup> and R<sup>4</sup> are identical or different and denote hydrogen, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, chinolyl, pyridyl, imidazolyl, 1,3-thiazolyl or thienyl, which are optionally substituted by identical or different substituents from the series comprising fluorine, chlorine, bromine, iodine, cyano, nitro or by straight-chain or

branched alkyl having up to 5 carbon atoms or denote straight-chain or branched alkyl or alkenyl each having up to 6 carbon atoms, and each of which is optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising trifluoromethyl, fluorine, chlorine, bromine, iodine, cyano, carboxy, hydroxy, straight-chain or branched alkoxy, alkoxy carbonyl or acyl each having up to 5 carbon atoms or by chinolyl, pyridyl, pyrazolyl, 1,3-thiadiazolyl, thienyl, imidazolyl or N-methyl-substituted imidazolyl and to which benzene can be fused, or by phenyl, where in all rings are optionally monosubstituted to disubstituted by identical or different substituents from the series comprising nitro, fluorine, chlorine, bromine, iodine, carboxy or straight-chain or branched alkyl or alkoxy carbonyl each having up to 5 carbon atoms,

or alkyl or alkenyl are substituted by a group of formula -CO-NR<sup>5</sup>R<sup>6</sup>

in which

R<sup>5</sup> and R<sup>6</sup> are identical or different and denote phenyl, benzyl, hydrogen, formyl, straight-chain or branched alkyl or alkenyl each having up to 5 carbon atoms, which are optionally substituted by carboxy, hydroxy or straight-chain or branched alkoxy carbonyl having up to 4 carbon atoms,

or

R<sup>3</sup> denotes acetyl, benzyl or tetrahydrofuranyl,

T represents an oxygen or sulfur atom

V represents a straight-chain or branched alkylene or alkenyl chain each having 2 to 6 carbon atoms,

W represents cyano, 1H-tetrazolyl or a group of a formula -CO-R<sup>7</sup>, -CO-NR<sup>8</sup>R<sup>9</sup>, -CONR<sup>10</sup>-SO<sub>2</sub>-R<sup>11</sup> or PO(OR<sup>12</sup>)(OR<sup>13</sup>),

in which

R<sup>7</sup> denotes hydroxyl, cyclopropyl oxy, cyclopentyl oxy, cyclohexyl oxy or straight-chain or branched alkoxy having up to 6 carbon atoms,

R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> are identical or different and denote hydrogen, benzyl, phenyl, straight-chain or branched alkyl or acyl each having up to 4 carbon atoms and which are optionally substituted by hydroxyl,

or

R<sup>9</sup> or R<sup>10</sup> denote hydroxyl,

R<sup>11</sup> denotes straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by phenyl or trifluoromethyl,

or

denotes phenyl, which is optionally substituted by substituents from the series comprising fluorine, chlorine, bromine, iodine, cyano, nitro or by straight-chain or branched alkyl having up to 4

	R <sup>12</sup> and R <sup>13</sup>	carbon atoms, are identical or different and represents hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,
5	R <sup>2</sup>	represents pyridyl, pyrryl, imidazolyl, pyrazolyl, thieryl, isothiazolyl, 1,3-thiazolyl or benzo[b]thiophenyl, wherein both rings are optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising hydroxyl, fluorine, chlorine, bromine, iodine, nitro, tetrazolyl, trifluoromethyl, trifluoromethoxy, difluoromethyl, difluoromethoxy, cyano, carboxy, straight-chain or branched alkyl, alkoxy, alkoxy carbonyl or acyl each having up to 6 carbon atoms or by a group of formula -NR <sup>14</sup> R <sup>15</sup> , -SR <sup>16</sup> , -SO <sub>2</sub> R <sup>17</sup> or -O-SO <sub>2</sub> R <sup>18</sup> .
10	R <sup>14</sup> and R <sup>15</sup>	in which have the first meaning shown above for R <sup>8</sup> and R <sup>9</sup> and are identical to the latter or different from the latter,
15	R <sup>16</sup> R <sup>17</sup> and R <sup>18</sup>	denotes straight-chain or branched alkyl having up to 4 carbon atoms, are identical or different and represent straight-chain or branched alkyl having up to 5 carbon atoms or phenyl, which is optionally substituted by trifluoromethyl, fluorine, chlorine, bromine or straight-chain or branched alkyl having up to 3 carbon atoms,
		and salts thereof.
20	3.	Heterocyclylcarbonyl substituted benzofuranyl- and thiophenyl-alkanecarboxylic acid derivatives according to claim 1, wherein
25	R <sup>1</sup>	represents hydrogen, fluorine, chlorine, bromine, nitro, trifluoromethyl or a group of a formula -OR <sup>3</sup> , or -SR <sup>4</sup> in which
30	R <sup>3</sup>	denotes hydrogen, tetrahydropyranyl, benzyl, acetyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, chinolyl, pyridyl, imidazolyl or thieryl, which are optionally substituted by identical or different substituents from the series comprising fluorine, chlorine, bromine, cyano, nitro or by straight-chain or branched alkyl having up to 4 carbon atoms or
35		denotes straight-chain or branched alkyl or alkenyl each having up to 5 carbon atoms, and each of which is optionally monosubstituted to disubstituted by identical or different substituents from the series comprising trifluoromethyl, fluorine, chlorine, bromine, cyano, carboxy, hydroxy, straight-chain or branched alkoxy, alkoxy carbonyl or acyl each having up to 4 carbon atoms or by chinolyl, pyridyl, imidazolyl or N-methyl-substituted imidazolyl, and to which benzene can be fused, or by phenyl, wherein all rings are optionally monosubstituted to disubstituted by identical or different substituents from the series comprising nitro, fluorine, chlorine, bromine, carboxy or straight-chain or branched alkyl, alkoxy carbonyl each having up to 4 carbon atoms, or alkyl or alkenyl are substituted by a group of formula -CO-NR <sup>5</sup> R <sup>6</sup>
40	R <sup>5</sup> and R <sup>6</sup>	in which are identical or different and denote phenyl, benzyl, hydrogen, formyl, straight-chain or branched alkyl each having up to 4 carbon atoms, which are optionally substituted by carboxy, hydroxy or straight-chain or branched alkoxy carbonyl having up to 3 carbon atoms,
45	R <sup>4</sup>	denotes straight-chain or branched alkyl having up to 4 carbon atoms,
	T	represents an oxygen or sulphur atom
	V	represents a straight-chain or branched alkylene or alkenylene chain having 2 to 5 carbon atoms,
	W	represents cyano, <sup>1</sup> H-tetrazolyl or a group of a formula -CO-R <sup>7</sup> or -CO-NR <sup>8</sup> R <sup>9</sup> ,
50	R <sup>7</sup>	in which denotes hydroxyl, cyclopropyloxy, cyclopentyloxy, cyclohexyloxy or straight-chain or branched alkoxy having up to 5 carbon atoms,
55	R <sup>8</sup> and R <sup>9</sup>	are identical or different and denote phenyl, benzyl, hydrogen, straight-chain or branched alkyl or acyl each having up to 4 carbon atoms, and
	R <sup>2</sup>	represents pyridyl, pyrryl, furyl, thieryl, 1,3-thiazolyl or benzo[b]thiophenyl, which are optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising hydroxyl, fluorine, chlorine, bromine, nitro, tetrazolyl, trifluoromethyl, trifluoromethoxy, difluoromethyl, difluoromethoxy, cyano, carboxy, straight-chain or branched alkyl, alkoxy, alkoxy carbonyl or acyl each having up to 5 carbon atoms or by a group of formula -NR <sup>14</sup> R <sup>15</sup> , -SR <sup>16</sup> or -SO <sub>2</sub> R <sup>17</sup> .

in which

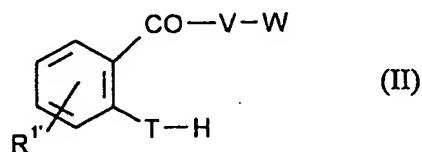
- $R^{14}$  and  $R^{15}$  have the meaning of  $R^8$  and  $R^9$ ,
- $R^{16}$  denotes straight-chain or branched alkyl having up to 3 carbon atoms,
- $R^{17}$  denotes straight-chain or branched alkyl having up to 3 carbon atoms or phenyl,

5

and salts thereof.

4. Heterocycl carbonyl substituted benzofuran-alkanecarboxylic acid derivatives according to claim 1 to 3 for the therapeutic use.
- 10 5. Process for the preparation of heterocycl carbonyl substituted benzofuran-alkanecarboxylic acid derivatives according to claim 1 to 3, characterized in that compounds of the general formula (II)

15



20

in which

- 25 T, V and W have the abovementioned meaning,

and

- 30  $R^1'$  represents a group of formula  $-OR^3'$ ,  
in which  
 $R^3'$  has the abovementioned meaning of  $R^3$ , but does not represent hydrogen,

are reacted with compounds of the general formula (III)

35



in which

- 40  $R^2$  has the abovementioned meaning

and

- 45 Y represents a typical leaving group such as, for example, chlorine, bromine, iodine, tosylate or mesylate, preferably bromine,

46

in inert solvents and in the presence of a base

and, then, if appropriate, the protective groups are split off,

the esters are hydrolysed, the acids are esterified with the appropriate alcohols in the presence of a catalyst or the compounds are alkylated

50

or the esters are directly reacted with amines or the free carboxylic acids, if appropriate in the presence of above and/or an auxiliary, an amidation or sulfonamidation follows.

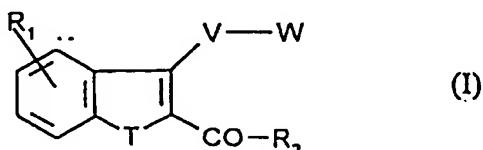
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6. Process according to claim 5 characterized in that it is carried out in a temperature range from +10°C to +150°C.
7. Composition containing at least one heterocycl carbonyl substituted benzofuran-alkanecarboxylic acid derivative according to claim 1 to 3 and a pharmacologically acceptable diluent.
8. Composition according to claim 7 for the treatment and prevention of acute and chronic inflammatory processes.

9. Use of heterocyclyc carbonyl substituted benzofuran-alkanecarboxylic acid derivatives according to claim 1 to 3 for the preparation of medicaments.
10. Use according to claim 9 for the preparation of medicaments for the treatment and prevention of acute and chronic inflammatory processes.

## 5 Patentansprüche

1. Heterocyclyc carbonyl-substituted Benzofuranyl- und -thiophenylalkan carboxylsäurederivate der allgemeinen Formel (I):



20 worin gilt:

R<sup>1</sup> stellt Wasserstoff, Halogen, eine Carboxyl-, Cyano-, Nitro-, Trifluormethyl- oder eine Gruppe der Formel -OR<sup>3</sup> oder -SR<sup>4</sup> dar,

worin gilt:

25 R<sup>3</sup> und R<sup>4</sup> sind gleich oder verschieden und bedeuten einen Cycloalkylrest mit 3 bis 6 Kohlenstoffatomen, Wasserstoff, einen 5- bis 7-gliedrigen gesättigten oder ungesättigten Heterozyklus mit bis zu 4 Heteroatomen aus den Reihen aus N, S und/oder O, der gegebenenfalls mit gleichen oder verschiedenen Substituenten aus den Reihen aus: Halogen, einer Cyano-, Nitro- oder einer geradkettigen oder verzweigten Alkylgruppe mit bis zu 6 Kohlenstoffatomen substituiert ist,

30 oder einen geradkettigen oder verzweigten Alkyl- oder Alkenylrest mit jeweils bis zu 8 Kohlenstoffatomen, die jeweils gegebenenfalls mit gleichen oder verschiedenen Substituenten aus den Reihen aus Trifluormethyl, Halogen, Cyano, Carboxy, Hydroxy, geradkettigem oder verzweigten Alkoxy, Alkoxycarbonyl oder aus Acyl mit jeweils bis zu 6 Kohlenstoffatomen oder mit einem 5- bis 7-gliedrigen gesättigten oder ungesättigten Heterozyklus mit bis zu 4 Heteroatomen aus den Reihen aus N, S und O, woran ein aromatischer Ring kondensiert sein kann, oder mit einem Phenylrest mono- bis trisubstituiert sind, worin alle Ringe gegebenenfalls mit gleichen oder verschiedenen Substituenten aus den Reihen aus einer Nitrogruppe, Halogen, einem Carboxy- oder geradkettigen oder verzweigten Alkyl- oder Alkoxy carbonylrest mit jeweils bis zu 6 Kohlenstoffatomen mono- bis trisubstituiert sind,

35 oder die Alkyl- oder Alkenylreste sind mit einer Gruppe der Formel -CO-NR<sup>5</sup>R<sup>6</sup> substituiert,

worin gilt:

40 R<sup>5</sup> und R<sup>6</sup> sind gleich oder verschieden und bedeuten Phenyl, Benzyl, Wasserstoff, Formyl, geradkettiges oder verzweigtes Alkyl oder Alkenyl mit jeweils bis zu 6 Kohlenstoffatomen, welche gegebenenfalls mit einer Carboxy-, Hydroxy-, geradkettigen oder verzweigten Alkoxy carbonylgruppe mit bis zu 6 Kohlenstoffatomen substituiert sind,

45 oder

R<sup>3</sup> bedeutet eine Hydroxyl-Schutzgruppe aus den Reihen aus: Trimethylsilyl, t-Butyldimethylsilyl, Benzyl, 4-Nitrobenzyl, 4-Methoxybenzyl, Acetyl, Tetrahydropyranyl und aus Benzoyl,

T stellt ein Sauerstoff- oder Schwefelatom dar,

50 V stellt eine geradkettige oder verzweigte Alkylen- oder Alkenylenkette mit jeweils 2 bis 8 Kohlenstoffatomen dar,

W stellt Cyano, 1H-Tetrazolyl oder eine Gruppe der Formel -CO-R<sup>7</sup>, -CO-NR<sup>8</sup>R<sup>9</sup>, -CONR<sup>10</sup>-SO<sub>2</sub>-R<sup>11</sup> oder PO(OR<sup>12</sup>)(OR<sup>13</sup>) dar,

worin gilt:

55 R<sup>7</sup> bedeutet Hydroxyl, Cycloalkyloxy mit 3 bis 7 Kohlenstoffatomen oder geradkettiges oder verzweigtes Alkoxy mit bis zu 8 Kohlenstoffatomen,

R<sup>8</sup>, R<sup>9</sup> und R<sup>10</sup> sind gleich oder verschieden und bedeuten Wasserstoff, Phenyl, Benzyl, geradkettiges oder verzweigtes Alkyl oder Acyl mit jeweils bis zu 8 Kohlenstoffatomen, welche gegebenenfalls mit einer Hydroxylgruppe substituiert sind,

oder

$R^8$  und  $R^9$  bedeuten eine Hydroxylgruppe,

$R^{11}$  bedeutet einen geradkettigen oder verzweigten Alkylrest mit bis zu 6 Kohlenstoffatomen, der gegebenenfalls mit einem Phenyl- oder Trifluormethylrest substituiert ist,

oder

einen Phenylrest, der gegebenenfalls mit Substituenten aus den Reihen aus Halogen, einer Cyano-, Nitro- oder einer geradkettigen oder verzweigten Alkylgruppe mit bis zu 6 Kohlenstoffatomen substituiert ist,

$R^{12}$  und  $R^{13}$  sind gleich oder verschieden und stellen Wasserstoff oder einen geradkettigen oder verzweigten Alkylrest mit bis zu 6 Kohlenstoffatomen dar,

10  $R^2$  stellt einen 5- bis 7-gliedrigen gesättigten oder ungesättigten Heterozyklus dar, der bis zu 3 Sauerstoff-, Schwefel- und/oder Stickstoffatome als Heteroatome enthalten und ferner an einen Benzolring kondensiert sein kann, worin beide Ringe gegebenenfalls mit gleichen oder verschiedenen Substituenten aus den Reihen aus einem Hydroxyl-, Halogen-, Nitro-, 1H-Tetrazolyl-, Trifluormethyl-, Trifluormethoxy-, Difluormethyl-, Difluormethoxy-, Cyano-, Carboxy-, geradkettigem oder verzweigten Alkyl-, Alkoxy-, Alkoxy carbonyl- oder aus einem Acylrest mit jeweils bis zu 8 Kohlenstoffatomen oder mit einer Gruppe der Formeln  $-NR^{14}R^{15}$ ,  $-SR^{16}$ ,  $-SO_2R^{17}$  oder  $-O-SO_2R^{18}$  mono- bis trisubstituiert sind,

worin gilt:

$R^{14}$  und  $R^{15}$  haben die erste Bedeutung, die oben für  $R^8$  und  $R^9$  angegeben ist, und sind gleich mit oder verschieden von den letzteren,

20  $R^{16}$  bedeutet einen geradkettigen oder verzweigten Alkylrest mit bis zu 6 Kohlenstoffatomen,

$R^{17}$  und  $R^{18}$  sind gleich oder verschieden und stellen einen geradkettigen oder verzweigten Alkylrest mit bis zu 6 Kohlenstoffatomen, einen Benzyl- oder Phenylrest dar, die gegebenenfalls mit einem Trifluormethylrest, Halogen oder einem geradkettigen oder verzweigten Alkylrest mit bis zu 6 Kohlenstoffatomen substituiert sind, und Salze davon.

25

2. Heterocyclcarbonyl-substituierte Benzofuranyl- und -thiophenylalkancarboxylsäurederivate gemäß Anspruch 1,

worin gilt:

30  $R^1$  stellt Wasserstoff, Fluor, Chlor, Brom, eine Nitro-, Trifluormethyl- oder eine Gruppe der Formel  $-OR^3$  oder  $-SR^4$  dar,

worin gilt:

35  $R^3$  und  $R^4$  sind gleich oder verschieden und bedeuten Wasserstoff, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Chinolyl, Pyridyl, Imidazolyl, 1,3-Thiazolyl oder Thienyl, welche gegebenenfalls mit gleichen oder verschiedenen Substituenten aus den Reihen aus Fluor, Chlor, Brom, Jod, einer Cyano- und aus einer Nitrogruppe oder mit einem geradkettigen oder verzweigten Alkylrest mit bis zu 5 Kohlenstoffatomen substituiert sind, oder

40 einen geradkettigen oder verzweigten Alkyl- oder Alkenylrest mit jeweils bis zu 6 Kohlenstoffatomen, die gegebenenfalls mit gleichen oder verschiedenen Substituenten aus den Reihen aus einem Trifluormethylrest, Fluor, Chlor, Brom, Jod, einem Cyano-, Carboxy-, Hydroxy-, geradkettigem oder verzweigten Alkoxy-, Alkoxy carbonyl- oder aus einem Acylrest mit jeweils bis zu 5 Kohlenstoffatomen oder mit einem Chinolyl-, Pyridyl-, Pyrazolyl-, 1,3-Thiadiazolyl-, Thienyl-, Imidazolyl- oder einem N-Methyl-substituierten Imidazolylrest, woran Benzol kondensiert sein kann, oder mit einem Phenylrest mono- bis trisubstituiert sind, worin alle Ringe gegebenenfalls mit gleichen oder verschiedenen Substituenten aus den Reihen aus einer Nitrogruppe, Fluor, Chlor, Brom, Jod, einer Carboxygruppe oder aus einem geradkettigen oder verzweigten Alkyl- oder Alkoxy carbonylrest mit jeweils bis zu 5 Kohlenstoffatomen mono- bis disubstituiert sind,

45

oder die Alkyl- oder Alkenylreste sind mit einer Gruppe der Formel  $-CO-NR^5R^6$  substituiert,

worin gilt:

50  $R^5$  und  $R^6$  sind gleich oder verschieden und bedeuten einen Phenyl-, Benzylrest, Wasserstoff, einen Formyl-, geradkettigen oder verzweigten Alkyl- oder Alkenylrest mit jeweils bis zu 5 Kohlenstoffatomen, die gegebenenfalls mit einer Carboxy-, Hydroxygruppe oder einem geradkettigen oder verzweigten Alkoxy carbonylrest mit bis zu 4 Kohlenstoffatomen substituiert sind,

oder

$R^3$  bedeutet einen Acetyl-, Benzyl- oder einen Tetrahydrofuranylrest,

T stellt ein Sauerstoff- oder Schwefelatom dar,

55

V stellt eine geradkettige oder verzweigte Alkylen- oder Alkenylenkette mit jeweils 2 bis 6 Kohlenstoffatomen dar,

W stellt eine Cyano-, 1H-Tetrazolyl- oder eine Gruppe einer Formel  $-CO-R^7$ ,  $-CO-NR^8R^9$ ,  $-CONR^{10}SO_2R^{11}$  oder  $-PO(OR^{12})(OR^{13})$  dar,

worin gilt:

R<sup>7</sup> bedeutet einen Hydroxyl-, Cyclopropoxy, Cyclopentyloxy-, Cyclohexyloxy- oder einen geradkettigen oder verzweigten Alkoxyrest mit bis zu 6 Kohlenstoffatomen,

5 R<sup>8</sup>, R<sup>9</sup> und R<sup>10</sup> sind gleich oder verschieden und bedeuten Wasserstoff, einen Benzyl-, Phenyl- und einen geradkettigen oder verzweigten Alkyl- oder Acylrest mit jeweils bis zu 4 Kohlenstoffatomen, die gegebenenfalls mit einem Hydroxylrest substituiert sind,

oder

R<sup>8</sup> oder R<sup>9</sup> bedeuten einen Hydroxylrest,

10 R<sup>11</sup> bedeutet einen geradkettigen oder verzweigten Alkylrest mit bis zu 5 Kohlenstoffatomen, der gegebenenfalls mit einem Phenyl- oder Trifluormethylrest substituiert ist, oder einen Phenylrest, der gegebenenfalls mit Substituenten aus den Reihen aus Fluor, Chlor, Brom, Jod, einer Cyano- und aus einer Nitrogruppe oder mit einem geradkettigen oder verzweigten Alkylrest mit bis zu 4 Kohlenstoffatomen substituiert ist,

15 R<sup>12</sup> und R<sup>13</sup> sind gleich oder verschieden und stellen Wasserstoff oder einen geradkettigen oder verzweigten Alkylrest mit bis zu 6 Kohlenstoffatomen dar,

R<sup>2</sup> stellt Pyridyl, Pyrryl, Imidazolyl, Pyrazolyl, Thienyl, Isothiazolyl, 1,3-Thiazolyl oder Benzo[b]thiophenyl dar, worin beide Ringe gegebenenfalls mit gleichen oder verschiedenen Substituenten aus den Reihen aus einem Hydroxylrest, Fluor, Chlor, Brom, Jod, einer Nitrogruppe, einem Tetrazolyl-, Trifluormethyl-, Trifluormethoxy-, Difluormethyl-, Difluormethoxy-, Cyano-, Carboxy-, geradkettigem oder verzweigten Alkyl-, Alkoxy-, Alkoxy carbonyl- oder aus einem Acylrest mit jeweils bis zu 6 Kohlenstoffatomen oder mit einer Gruppe der Formel -NR<sup>14</sup>R<sup>15</sup>, -SR<sup>16</sup>, -SO<sub>2</sub>R<sup>17</sup> oder -O-SO<sub>2</sub>R<sup>18</sup> mono- bis trisubstituiert sind,

worin gilt:

R<sup>14</sup> und R<sup>15</sup> haben die erste Bedeutung, die oben für R<sup>8</sup> und R<sup>9</sup> angegeben ist, und sind gleich mit oder verschieden von den letzteren,

25 R<sup>16</sup> bedeutet einen geradkettigen oder verzweigten Alkylrest mit bis zu 4 Kohlenstoffatomen,

R<sup>17</sup> und R<sup>18</sup> sind gleich oder verschieden und stellen einen geradkettigen oder verzweigten Alkylrest mit bis zu 5 Kohlenstoffatomen oder einen Phenylrest dar, der gegebenenfalls mit einem Trifluormethylrest, Fluor, Chlor, Brom oder einem geradkettigen oder verzweigten Alkylrest mit bis zu 3 Kohlenstoffatomen substituiert ist,

30 und Säze davon.

### 3. Heterocyclcarbonyl-substituierte Benzofuranyl- und -thiophenylalkancarboxylsäurederivate gemäß Anspruch 1, worin gilt:

35 R<sup>1</sup> stellt Wasserstoff, Fluor, Chlor, Brom, eine Nitro-, Trifluormethyl- oder eine Gruppe der Formel -OR<sup>3</sup> oder -SR<sup>4</sup> dar,

worin gilt:

R<sup>3</sup> bedeutet Wasserstoff, Tetrahydropyranyl, Benzyl, Acetyl, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Chinolyl, Pyridyl, Imidazolyl oder Thienyl, welche mit gleichen oder verschiedenen Substituenten aus den Reihen aus Fluor, Chlor, Brom, einer Cyano- und aus einer Nitrogruppe oder mit einem geradkettigen oder verzweigten Alkylrest mit bis zu 4 Kohlenstoffatomen substituiert sind, oder

40 einen geradkettigen oder verzweigten Alkyl- oder Alkenylrest mit jeweils bis zu 5 Kohlenstoffatomen, welche gegebenenfalls mit gleichen oder verschiedenen Substituenten aus den Reihen aus einem Trifluormethylrest, Fluor, Chlor, Brom, einem Cyano-, Carboxy-, Hydroxy-, geradkettigem oder verzweigten Alkoxy-, Alkoxy carbonyl- oder aus einem Acylrest mit jeweils bis zu 4 Kohlenstoffatomen oder mit einem Chinolyl-, Pyridyl-, Imida-

45 zolyl- oder einem N-Methyl-substituierten Imidazolylrest, an welche Benzol kondensiert sein kann, oder mit einem Phenylrest mono- bis disubstituiert sind, worin alle Ringe gegebenenfalls mit gleichen oder verschiedenen Substituenten aus den Reihen aus einer Nitrogruppe, Fluor, Chlor, Brom, einem Carboxy- oder geradket- tigen oder verzweigten Alkyl- und aus einem Alkoxy carbonylrest mit jeweils bis zu 4 Kohlenstoffatomen mono- bis distubstituiert sind,

50 oder die Alkyl- oder Alkenylreste sind mit einer Gruppe der Formel -CO-NR<sup>5</sup>R<sup>6</sup> substituiert,

worin gilt:

R<sup>5</sup> und R<sup>6</sup> sind gleich oder verschieden und bedeuten einen Phenyl-, Benzylrest, Wasserstoff, einen Formyl-, geradkettigen oder verzweigten Alkylrest mit jeweils bis zu 4 Kohlenstoffatomen, welche gegebenenfalls mit einer Carboxy-, Hydroxy- oder einer geradkettigen oder verzweigten Alkoxy carbonylgruppe mit bis zu 3 Kohlenstoffatomen substituiert sind,

55 R<sup>4</sup> bedeutet einen geradkettigen oder verzweigten Alkylrest mit bis zu 4 Kohlenstoffatomen,

T stellt Sauerstoff oder Schwefel dar.

V stellt eine geradkettige oder verzweigte Alkylen- oder Alkenylenkette mit 2 bis 5 Kohlenstoffatomen dar,  
W stellt eine Cyano-, 1H-Tetrazolyl- oder eine Gruppe der Formel -CO-NR<sup>8</sup>R<sup>9</sup> oder -CO-R<sup>7</sup> dar,  
worin gilt:

R<sup>7</sup> bedeutet einen Hydroxyl-, Cyclopropoxy-, Cyclopentyloxy-, Cyclohexyloxy- oder einen geradkettigen  
oder verzweigten Alkoxyrest mit bis zu 5 Kohlenstoffatomen,

R<sup>8</sup> und R<sup>9</sup> sind gleich oder verschieden und bedeuten einen Phenyl-, Benzylrest, Wasserstoff, einen verzweigten oder geradkettigen Alkyl- oder Acylrest mit jeweils bis zu 4 Kohlenstoffatomen, und

R<sup>2</sup> stellt Pyridyl, Pyrryl, Furyl, Thienyl, 1,3-Thiazolyl oder Benzo[b]thiophenyl dar, welche gegebenenfalls mit gleichen oder verschiedenen Substituenten aus den Reihen aus einem Hydroxylrest, Fluor, Chlor, Brom, einer Nitrogruppe, einem Tetrazolyl-, Trifluormethyl-, Trifluormethoxy-, Difluormethyl-, Difluormethoxy-, Cyano-, Carboxy-, geradkettigem oder verzweigten Alkyl-, Alkoxy-, Akoxy carbonyl- oder aus einem Acylrest mit jeweils bis zu 5 Kohlenstoffatomen oder mit einer Gruppe der Formel -NR<sup>14</sup>R<sup>15</sup>, -SR<sup>16</sup> oder -SO<sub>2</sub>R<sup>17</sup> mono- bis trisubstituiert sind,

worin gilt:

R<sup>14</sup> und R<sup>15</sup> haben die Bedeutung von R<sup>8</sup> und R<sup>9</sup>,

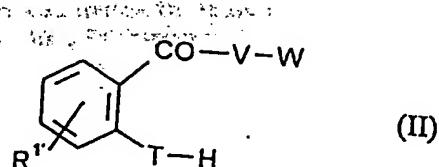
R<sup>16</sup> bedeutet einen geradkettigen oder verzweigten Alkylrest mit bis zu 3 Kohlenstoffatomen,

R<sup>17</sup> bedeutet einen geradkettigen oder verzweigten Alkylrest mit bis zu 3 Kohlenstoffatomen oder einen Phenylrest,

und Salze davon.

4. Heterocyclcarbony-substituierte Benzofuranalkancarboxylsäurederivate gemäß einem der Ansprüche 1 bis 3 zur therapeutischen Verwendung.
- 25 5. Verfahren zur Herstellung Heterocyclcarbonylsubstituierter Benzofuranalkancarboxylsäurederivate gemäß einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß

Verbindungen der allgemeinen Formel (II):



worin

T, V und W die oben angegebene Bedeutung haben,

und

R¹ eine Gruppe der Formel -OR<sup>3</sup> darstellt,

worin

R<sup>3</sup> die oben angegebene Bedeutung von R<sup>3</sup> hat, jedoch nicht Wasserstoff darstellt,

mit Verbindungen der allgemeinen Formel (III):



worin

R<sup>2</sup> die oben angegebene Bedeutung hat

und

Y eine typische Abgangsgruppe wie z.B. Chlor, Brom, Jod, Tosylat oder Mesylat, vorzugsweise Brom, darstellt, in inerten Lösungsmitteln und in der Gegenwart einer Base zur Reaktion gebracht werden,

und dann, gegebenenfalls, die Schutzgruppen abgespalten,

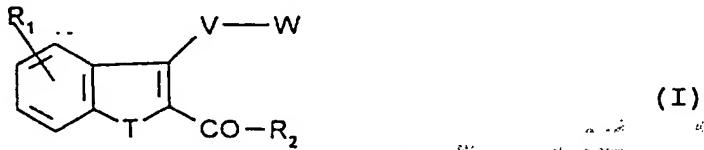
die Ester hydrolysiert, die Säuren mit den geeigneten Alkoholen in der Gegenwart eines Katalysators verestert oder die Verbindungen alkyliert oder die Ester direkt mit Aminen umgesetzt oder die freien Carboxylsäuren, gegebenenfalls in der Gegenwart eines obigen und/oder eines weiteren Hilfsstoffs, amidiert oder sulfoamidiert

werden.

6. Verfahren gemäß Anspruch 5,  
dadurch gekennzeichnet, daß  
es in einem Temperaturbereich von +10 bis +150°C durchgeführt wird.
- 5 7. Zusammensetzung, enthaltend mindestens ein Heterocyclcarbonyl-substituiertes Benzofuranalkancarboxylsäurederivat gemäß einem der Ansprüche 1 bis 3 und ein pharmakologisch geeignetes Verdünnungsmittel.
- 10 8. Zusammensetzung gemäß Anspruch 7 zur Behandlung und Vorbeugung akuter und chronischer Entzündungen.
9. Verwendung Heterocyclcarbonyl-substituierter Benzofuranalkancarboxylsäurederivate gemäß einem der Ansprüche 1 bis 3 zur Herstellung von Medikamenten.
- 15 10. Verwendung gemäß Anspruch 9 zur Herstellung von Medikamenten zur Behandlung und Vorbeugung akuter und chronischer Entzündungen.

#### Revendications

- 20 1. Dérivés d'acides benzofuranyl- et benzothiophénylalcanecarboxyliques substitués par des radicaux hétérocyclcarbonyle de formule générale (I)



30 dans laquelle

R<sup>1</sup> représente un atome d'hydrogène, d'halogène, un radical carboxyle, cyano, nitro, trifluorométhyle ou un radical de formule -OR<sup>3</sup> ou -SR<sup>4</sup>,

35 dans lesquelles

R<sup>3</sup> et R<sup>4</sup> sont identiques ou différents et représentent un radical cycloalcoyle ayant 3 à 6 atomes de carbone, un atome d'hydrogène, un hétérocycle saturé ou insaturé de 5 à 7 membres ayant jusqu'à 4 hétéroatomes de la série comprenant N, S et O, qui est facultativement substitué par des substituants identiques ou différents de la série comprenant les substituants halogéno, cyano, nitro ou par un radical alcoyle à chaîne droite ou ramifiée ayant jusqu'à 6 atomes de carbone ou représentent un radical alcoyle ou un radical alcényle à chaîne droite ou ramifiée ayant chacun jusqu'à 8 atomes de carbone, et dont chacun est facultativement monosubstitué à trisubstitué par des substituants identiques ou différents de la série comprenant les groupes trifluorométhyle, halogéno, cyano, carboxy, hydroxy, alcoxy alcoxycarbonyle ou acyle à chaîne droite ou ramifiée, chacun ayant jusqu'à 6 atomes de carbone ou par un hétérocycle saturé ou insaturé de 5 à 7 membres ayant jusqu'à 4 hétéroatomes de la série comprenant N, S et O et auquel un cycle aromatique peut être accolé,

40 ou par un radical phényle, tous les cycles étant facultativement monosubstitués à trisubstitués par des substituants identiques ou différents de la série comprenant les substituants nitro, halogéno, carboxy ou alcoyle ou alcoxycarbonyle à chaîne droite ou ramifiée, chacun ayant jusqu'à 6 atomes de carbone,

45 ou les radicaux alcoyle ou alcényle sont substitués par un radical de formule -CO-NR<sup>5</sup>R<sup>6</sup> dans laquelle

R<sup>5</sup> et R<sup>6</sup> sont identiques ou différents et représentent un radical phényle, benzyle, un atome d'hydrogène, un radical formyle ou alcoyle ou alcényle à chaîne droite ou ramifiée ayant chacun jusqu'à 6 atomes de carbone et qui sont facultativement substitués par les substituants carboxy, hydroxy, alcoxycarbonyle à chaîne droite ou ramifiée ayant jusqu'à 6 atomes de carbone, ou

50 R<sup>3</sup> représente un radical protecteur d'hydroxyle, de la série comprenant les radicaux triméthylsilyle, t-butylidéméthylsilyle, benzyle, 4-nitrobenzyle, 4-méthoxybenzyle, acétyle, tétrahydropyranyle et benzoyle,

55 T représente un atome d'oxygène ou de soufre,

V représente un groupe alcoylène ou un groupe alcénylène à chaîne droite ou ramifiée chacun ayant 2 à 8 atomes de carbone,

W représente un radical cyano, 1H-tétrazolyde ou un radical de formule -CO-R<sup>7</sup>, -CO-NR<sup>8</sup>R<sup>9</sup>, -CONR<sup>10</sup>-SO<sub>2</sub>-R<sup>11</sup> ou PO(OR<sup>12</sup>)(OR<sup>13</sup>), dans lesquelles

5 R<sup>7</sup> représente un radical hydroxyle, cycloalcoyloxy ayant jusqu'à 3 à 7 atomes de carbone ou un alcoxy à chaîne droite ou ramifiée ayant jusqu'à 8 atomes de carbone,

R<sup>8</sup>, R<sup>9</sup> et R<sup>10</sup> sont identiques ou différents et représentent un atome d'hydrogène, un radical phényle, benzyle, alcoyle ou acyle à chaîne droite ou ramifiée, chacun ayant jusqu'à 6 atomes de carbone et qui sont facultativement substitués par un radical hydroxyle,

ou

10 R<sup>8</sup> et R<sup>9</sup> représentent un radical hydroxyle, R<sup>11</sup> représente un radical alcoyle à chaîne droite ou ramifiée ayant jusqu'à 6 atomes de carbone, qui est facultativement substitué par un radical phényle ou trifluorométhyle, ou représente un radical phényle qui est facultativement substitué par des substituants de la série comprenant un halogène, un radical cyano, nitro, ou par un alcoyle à chaîne droite ou ramifiée ayant jusqu'à 6 atomes de carbone,

15 R<sup>12</sup> et R<sup>13</sup> sont identiques ou différents et représentent un atome d'hydrogène ou un radical alcoyle à chaîne droite ou ramifiée ayant jusqu'à 6 atomes de carbone,

R<sup>2</sup> représente un hétérocycle de 5 à 7 membres saturé ou insaturé, qui peut contenir jusqu'à trois atomes d'oxygène, de soufre et/ou d'azote comme hétéroatomes et auquel en plus un cycle benzénique peut être accolé et où les deux cycles sont facultativement monosubstitués à trisubstitués par des substituants identiques ou différents de la série comprenant les substituants hydroxyle, halogéno, nitro, 1H-tétrazolyde, trifluorométhyle, trifluorométhoxy, difluorométhyle, difluorométhoxy, cyano, carboxy, alcoyle à chaîne droite ou ramifiée, alcoxy, alcoxycarbonyle ou acyle ayant jusqu'à 8 atomes de carbone, ou par un radical de formule -

20 NR<sup>14</sup>R<sup>15</sup>, -SR<sup>16</sup>, SO<sub>2</sub>R<sup>17</sup> ou -O-SO<sub>2</sub>-R<sup>18</sup>, dans lesquelles

25 R<sup>14</sup> et R<sup>15</sup> ont les significations montrées ci-dessus en premier lieu pour R<sup>8</sup> et R<sup>9</sup> et sont identiques à ceux-ci ou différents de ceux-ci, R<sup>16</sup> représente un alcoyle à chaîne droite ou ramifiée ayant jusqu'à 6 atomes de carbone, R<sup>17</sup> et R<sup>18</sup> sont identiques ou différents et représentent un alcoyle à chaîne droite ou ramifiée ayant jusqu'à 6 atomes de carbone, benzyle ou phényle qui sont facultativement substitués par les substituants trifluorométhyle, halogéno ou alcoyle à chaîne droite ou ramifiée ayant jusqu'à 6 atomes de carbone,

30 et les sels de ceux-ci.

2. Dérivés d'acides benzofuranyl- et benzothiophénylalcancarboxyliques substitués par des radicaux hétérocycl-carbonyle selon la revendication 1, où R<sup>1</sup> représente un atome d'hydrogène, de fluor, de chlore, de brome, un groupe nitro, trifluorométhyle ou un radical de formule -OR<sup>3</sup> ou -SR<sup>4</sup>.

35 dans lesquelles

R<sup>3</sup> et R<sup>4</sup> sont identiques ou différents et représentent un atome d'hydrogène, un radical cyclopropyle, cyclobutyle, cyclopentyle, cyclohexyle, quinolyde, pyridyle, imidazolyde, 1,3-thiazolyde ou thiényle, qui sont facultativement substitués par des substituants identiques ou différents de la série comprenant un atome de fluor, de chlore, de brome, d'iode, un radical cyano, nitro, ou par un alcoyle à chaîne droite ou ramifiée ayant jusqu'à 5 atomes de carbone ou

40 représentent un radical alcoyle ou un radical alcényle à chaîne droite ou ramifiée ayant chacun jusqu'à 6 atomes de carbone, et dont chacun est facultativement monosubstitué à trisubstitué par des substituants identiques ou différents de la série comprenant les substituants trifluorométhyle, fluor, chlore, brome, iode, cyano, carboxy, hydroxy, alcoxy, alcoxycarbonyle ou acyle à chaîne droite ou ramifiée chacun ayant jusqu'à 5 atomes de carbone ou par un quinolyde, pyridyle, pyrazolyde, 1,3-thiadiazolyde, thiényle, imidazolyde, ou imidazolyde N-méthyle substitué et auquel un cycle benzénique peut être accolé,

45 ou par un radical phényle, tous les anneaux étant facultativement monosubstitués à disubstitués par des substituants identiques ou différents de la série comprenant les radicaux nitro, fluor, chlore, brome, iode, carboxy ou alcoyle ou alcoxycarbonyle à chaîne droite ou ramifiée, chacun ayant jusqu'à 5 atomes de carbone, ou alcoyle ou alcényle sont substitués par un radical de formule -CO-NR<sup>5</sup>R<sup>6</sup>

ou

50 R<sup>5</sup> et R<sup>6</sup> sont identiques ou différents et représentent un radical phényle, benzyle, un atome d'hydrogène, un radical formyle, alcoyle ou alcényle à chaîne droite ou ramifiée ayant chacun jusqu'à 5 atomes de carbone, qui sont facultativement substitués par les substituants carboxy, hydroxy ou alcoxycarbonyle à chaîne droite ou ramifiée ayant jusqu'à 4 atomes de carbone,

ou

55 R<sup>3</sup> représente un radical acétyle, benzyle ou tétrahydrofuranyl

T représente un atome d'oxygène ou de soufre,

V représente un groupe alcoyle ou un groupe alcényle à chaîne droite ou ramifiée chacun ayant 2 à 6 atomes de carbone,

W représente un cyano, 1H-tétrazolyte ou un radical -CO-R<sup>7</sup>, -CO-NR<sup>8</sup>R<sup>9</sup>, -CONR<sup>10</sup>-SO<sub>2</sub>-R<sup>11</sup> ou PO(OR<sup>12</sup>)(OR<sup>13</sup>),

ou

R<sup>7</sup> représente un radical hydroxyle, cyclopropoxy, cyclopentyloxy, cyclohexyloxy, ou un alcoxy à chaîne droite ou ramifiée ayant jusqu'à 6 atomes de carbone,

R<sup>8</sup>, R<sup>9</sup> et R<sup>10</sup> sont identiques ou différents et représentent un atome d'hydrogène, un radical benzyle, phényle, alcoyle ou acyle à chaîne droite ou ramifiée chacun ayant jusqu'à 4 atomes de carbone et qui sont facultativement substitués par un radical hydroxyle,

ou

R<sup>8</sup> et R<sup>9</sup> représentent un radical hydroxyle, R<sup>11</sup> représente un radical alcoyle à chaîne droite ou ramifiée ayant jusqu'à 5 atomes de carbone, qui est facultativement substitué par un radical phényle ou trifluorométhyle, ou

représente un radical phényle qui est facultativement substitué par des substituants de la série comprenant un atome de fluor, de chlore, de brome, d'iode, un cyano, nitro, ou par un alcoyle à chaîne droite ou ramifiée ayant jusqu'à 4 atomes de carbone,

R<sup>12</sup> et R<sup>13</sup> sont identiques ou différents et représentent un atome d'hydrogène ou un radical alcoyle à chaîne droite ou ramifiée ayant jusqu'à 6 atomes de carbone,

R<sup>2</sup> représente un radical pyridyle, pyrryle, imidazolyte, pyrazolyle, thiényle, isothiazolyle, 1,3-thiazolyle ou benzo[b]thio-phényle, où les deux cycles sont facultativement monosubstitués à trisubstitués par des substituants identiques ou différents de la série comprenant un radical hydroxyle, un atome de fluor, de chlore, de brome, d'iode, un radical nitro, tétrazolyte, trifluorométhyle, trifluorométhoxy, difluorométhyle, difluorométhoxy,

cyano, carboxy, alcoyle, alcoxy, alcoxycarbonyle ou acyle à chaîne droite ou ramifiée, ayant chacun jusqu'à 6 atomes de carbone ou par un radical de formule -NR<sup>14</sup>R<sup>15</sup>, -SR<sup>16</sup>, SO<sub>2</sub>R<sup>17</sup> ou -O-SO<sub>2</sub>-R<sup>18</sup>,

dans lesquelles

R<sup>14</sup> et R<sup>15</sup> ont les significations montrées en premier lieu ci-dessus pour R<sup>8</sup> et R<sup>9</sup> et sont identiques à ceux-ci ou différents de ceux-ci, R<sup>16</sup> représente un radical alcoyle à chaîne droite ou ramifiée ayant jusqu'à 4 atomes de carbone,

R<sup>17</sup> et R<sup>18</sup> sont identiques ou différents et représentent un radical alcoyle à chaîne droite ou ramifiée ayant jusqu'à 5 atomes de carbone, ou phényle qui est facultativement substitué par un radical trifluorométhyle, un atome de fluor, de chlore, de brome, d'iode ou un radical alcoyle à chaîne droite ou ramifiée ayant jusqu'à 3 atomes de carbone,

et les sels de ceux-ci.

3. Dérivés d'acides benzofuranyl- et benzothiophénylalcanecarboxyliques substitués par des radicaux hétérocycl-carbonyle selon la revendication 1,  
dans lesquels

R<sup>1</sup> représente un atome d'hydrogène, de fluor, de chlore, de brome, un radical nitro, trifluorométhyle ou un radical de formule -OR<sup>3</sup> ou -SR<sup>4</sup>,

dans lesquelles

R<sup>3</sup> représente un atome d'hydrogène, un radical tétrahydronpyranyle, benzyle, acétyle, cyclopropyle, cyclobutyle, cyclopentyle, cyclohexyle, quinolyte, pyridyle, imidazolyte ou thiényle, qui sont facultativement substitués par des substituants identiques ou différents de la série comprenant un atome de fluor, de chlore, de brome, un radical cyano, nitro ou par un alcoyle à chaîne droite ou ramifiée ayant jusqu'à 4 atomes de carbone ou

représente un radical alcoyle ou un radical alcényle à chaîne droite ou ramifiée ayant chacun jusqu'à 5 atomes de carbone, et dont chacun est facultativement monosubstitué à disubstitué par des substituants identiques ou différents de la série comprenant un radical trifluorométhyle, un atome de fluor, de chlore, de brome, un radical cyano, carboxy, hydroxy, alcoxy, alcoxycarbonyle ou acyle à chaîne droite ou ramifiée, chacun ayant jusqu'à 4 atomes de carbone ou par un radical quinolyte, pyridyle, imidazolyte ou imidazolyle N-méthyle substitué et auquel un cycle benzénique peut être accolé,

ou par un radical phényle, tous les cycles étant facultativement monosubstitués à disubstitués par des substituants identiques ou différents de la série comprenant les substituants nitro, fluor, chlore, brome, carboxy ou alcoyle ou alcoxycarbonyle à chaîne droite ou ramifiée chacun ayant jusqu'à 4 atomes de carbone, ou les radicaux alcoyle ou alcényle sont substitués par un radical de formule -CO-NR<sup>5</sup>R<sup>6</sup>

ou

R<sup>5</sup> et R<sup>6</sup> sont identiques ou différents et représentent un radical phényle, benzyle, un atome d'hydrogène, un

radical formyle, alcoyle à chaîne droite ou ramifiée ayant chacun jusqu'à 4 atomes de carbone, qui sont facultativement substitués par un substituant carboxy, hydroxy ou alcooxycarbonyle à chaîne droite ou ramifiée ayant jusqu'à 3 atomes de carbone,

R<sup>4</sup> représente un radical alcoyle à chaîne droite ou ramifiée ayant jusqu'à 4 atomes de carbone,

T représente un atome d'oxygène ou de soufre,

V représente un radical alcoylène ou un radical alcénylène à chaîne droite ou ramifiée chacun ayant 2 à 5 atomes de carbone,

W représente un radical cyano, 1H-tétrazolylique ou un radical -CO-R<sup>7</sup>, -CO-NR<sup>8</sup>R<sup>9</sup>,

où

R<sup>7</sup> représente un radical hydroxyle, cyclopropyloxy, cyclopentyloxy, cyclohexyloxy, ou un radical alcoxy à chaîne droite ou ramifiée ayant jusqu'à 5 atomes de carbone,

R<sup>8</sup> et R<sup>9</sup> sont identiques ou différents et représentent un radical benzyle, phényle, un atome d'hydrogène, un radical alcoyle ou acyle à chaîne droite ou ramifiée chacun ayant jusqu'à 4 atomes de carbone, et

R<sup>2</sup> représente un radical pyridyle, pyrryle, furyle, thiényle, 1,3-thiazolylique ou benzo[b]thiophényle, qui sont facultativement monosubstitués à trisubstitués par des substituants identiques ou différents de la série comprenant un radical hydroxyle, un atome de fluor, de chlore, de brome, un radical nitro, tétrazolylique, trifluorométhyle, trifluorométhoxy, difluorométhyle, difluorométhoxy, cyano, carboxy, alcoyle, alcoxy, alcooxycarbonyle ou acyle à chaîne droite ou ramifiée, ayant jusqu'à 5 atomes de carbone ou par un radical de formule -NR<sup>14</sup>R<sup>15</sup>, -SR<sup>16</sup>,

SO<sub>2</sub>R<sup>17</sup>,

dans lesquelles

R<sup>14</sup> et R<sup>15</sup> ont les significations de R<sup>8</sup> et R<sup>9</sup>,

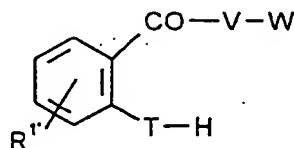
R<sup>16</sup> représente un radical alcoyle à chaîne droite ou ramifiée ayant jusqu'à 3 atomes de carbone,

R<sup>17</sup> représente un radical alcoyle à chaîne droite ou ramifiée ayant jusqu'à 3 atomes de carbone, ou un radical phényle,

et les sels de ceux-ci.

4. Dérivés d'acides benzofurane-alcanecarboxyliques substitués par des radicaux hétérocyclycarbonyliques selon les revendications 1 à 3 pour l'utilisation thérapeutique.

5. Procédé pour la préparation de dérivés d'acides benzofurane-alcanecarboxyliques substitués par des radicaux hétérocyclycarbonylique selon les revendications 1 à 3, caractérisé en ce que des composés de formule générale (II)



(II)

45 dans laquelle

T, V et W ont les significations ci-dessus mentionnées,

et

R<sup>1</sup> représente un radical de formule -OR<sup>3</sup>,

dans laquelle

R<sup>3</sup> a la signification ci-dessus mentionnée de R<sup>3</sup>, mais ne représente pas un atome d'hydrogène, sont mis à réagir avec des composés de la formule générale (III)



(III)

55

dans laquelle

R<sup>2</sup> a la signification ci-dessus

et

Y représente un radical partant typique comme par exemple, un atome de chlore, de brome, d'iode, un radical tosylate ou mésylate, de préférence un atome de brome,  
dans des solvants inertes et en présence d'une base et, ensuite, si souhaité, les radicaux protecteurs sont éliminés.

5 les esters sont hydrolysés, les acides sont estérifiés avec les alcools appropriés en présence d'un catalyseur ou les composés sont alcoyés  
ou les esters sont directement mis à réagir avec les amines ou les acides carboxyliques libres, si c'est approprié, en présence des composés ci-dessus et/ou un auxiliaire, une amidation ou sulfonamidation suit.

- 10 6. Procédé selon la revendication 5 caractérisé en ce que l'intervalle de température est de +10°C à +150°C.
7. Composition contenant au moins un dérivé d'acide benzofurane-alcanecarboxylique substitué par des radicaux hétérocyclcarbonyle selon les revendications 1 à 3 et un diluant pharmacologiquement acceptable.
- 15 8. Composition selon la revendication 7 pour le traitement et la prévention de processus inflammatoires aigus et chroniques.
9. Utilisation de dérivés d'acides benzofuranealcanecarboxyliques substitués par des radicaux hétérocyclcarbonyle selon les revendications 1 à 3 pour la préparation de médicaments.
- 20 10. Utilisation selon la revendication 9 pour la préparation de médicaments pour le traitement et la prévention de procédés inflammatoires aigus et chroniques.

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